REMARKS

The Office Action dated December 22, 2006 has been received and carefully considered. In this response, the specification and claims 12-15 have been amended and claim 59 has been added. Entry of the amendments to the specification and claims 12-15 and the addition of claim 59 is respectfully requested. Reconsideration of the outstanding objections/rejections in the present application is also respectfully requested based on the following remarks.

I. THE OBJECTION TO THE SPECIFICATION

On page 2 of the Office Action, the specification was objected to for failing to comply with the sequence listing requirements of 37 C.F.R. §§ 1.821 through 1.825. On page 3 of the Office Action, paragraph [0071] was objected to for including an active hyperlink.

Responsive to these objections, Applicants have amended the specification. Specifically, Applicants have amended relevant portions of the Detailed Description with reference to sequence listings submitted concurrently herewith both in paper form and in computer readable form. Applicants have replaced paragraph [0071] with a deactivated hyperlink.

In view of the foregoing, it is respectfully requested that the aforementioned objection to the specification be withdrawn.

II. THE NON-STATUTORY SUBJECT MATTER REJECTION OF CLAIMS 12-23

On page 3 of the Office Action, claims 12-23 were rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter. The Examiner asserts that claims 12-23 are not limited to tangible embodiments because they fail to produce "a real world result." Applicants respectfully submit that there is no such "tangible" requirement on patentable subject matter as

long as the claimed invention as a whole accomplishes a practical application. It is undisputed that the claimed invention as a whole produces useful and concrete results — scoring information associated with peptide matches. Therefore, the claimed invention is directed to patentable subject matter.

Notwithstanding the foregoing, Applicants have added a general "outputting" step to claim 12, which ensures that the claimed method produce "tangible" results. It should be noted that the information can be output via either a human-machine interface or a machine-machine interface.

In view of the foregoing, it is respectfully requested that the aforementioned non-statutory subject matter rejection of claims 12-23 be withdrawn.

III. THE INDEFINITENESS REJECTION OF CLAIMS 12-24

On page 4 of the Office Action, claims 12-24 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the invention. The Examiner points out that claim 12 recites "*s* is a peptide sequence" but does not specify whether it refers to an experimental or candidate peptide. Responsive to this rejection, Applicants have amended claim 12 to indicate that "*s* is a peptide sequence associated with the candidate peptide."

In view of the foregoing, it is respectfully requested that the aforementioned indefiniteness rejection of claims 12-24 be withdrawn.

IV. THE OBVIOUSNESS REJECTION OF CLAIMS 12-15 AND 18-24

On page 5 of the Office Action, claims 12-15 and 18-24[1] were rejected under 35 U.S.C. §103(a) as being unpatentable over Bafna (2001; NPL #28) in view of Blumenfeld (U.S. Patent No. 6,432,648). This rejection is hereby respectfully traversed.

Under 35 U.S.C. § 103, the Patent Office bears the burden of establishing a prima facie case of obviousness. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). The Patent Office can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of references. Id. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984). That is, under 35 U.S.C. § 103, teachings of references can be combined only if there is some suggestion or motivation to do so. Id.. However, the motivation cannot come from the applicant's invention itself. In re Oetiker, 977 F.2d 1443, 1447, 24 USPQ2d 1443, 1446 (Fed. Cir. 1992). Rather, there must be some reason, suggestion, or motivation ound in the prior art whereby a person of ordinary skill in the art would make the combination. Id.

Regarding claim 12, the Examiner asserts that Bafna teaches software programs for analyzing MS data that include all the claim elements except the use of likelihood ratio for scoring. The Examiner further asserts that it would be obvious to combine the three-module

[1] It appears that claims 16 and 17 were not specifically rejected for obviousness.

matching-and-scoring method taught by Bafna with the teaching of likelihood ratio matching technique taught by Blumenfeld. These assertions are incorrect for the following reasons.

In order to properly compare the cited references with the present invention, it is helpful to have an overview of their respective disclosures.

In its "Earlier Work" section (S14, col. 2), Bafna summarizes the then-existing methods for analyzing tandem MS data into three steps — Interpretation, Filtering, and Scoring, which is merely a high-level generalization without much detail. Bafna then summarized an improved two-step stochastic process for generating MS/MS spectra (S15, col. 2, second paragraph). "The first step involves generation of fragments from a peptide, according to a probability distribution estimated from many training samples. The second step involves the generation of a spectrum from the fragments according to the distribution of instrument measurement error." Id. Implementation details are then given in the next few pages, such as defining fragmentation space $\phi(p)$ of a peptide p and estimating fragmentation probabilities. As noted in the Specification of the present application (paragraph [0008]), Bafna [and Edwards] "*consider only fragment masses, do not rely on parent peptide charge, and also do not calculate the likelihood ratio of observing a correct match versus observing a random match. Bafna and Edwards do not attempt to detect global patterns corresponding to structural constraints resulting from physical principles, like series of consecutive fragment matches.*"

Blumenfeld is concerned with an entirely different field, namely the field of pharmacogenomics, and is primarily directed to biallelic markers that are located in or in the vicinity of genes. The Examiner cites Blumenfeld for the sole purpose of supplementing Bafna with the likelihood ratio matching technique.

The present invention, as recited in claim 12, is directed to a method for scoring peptide matches. A significant improvement over the prior methods involves the establishment of a precise mathematical framework that facilitates exploitation of extensive information available from an MS/MS spectrum. Specifically, the claimed method includes a step of "*defining an extended match E based on the information associated with the experimental peptide and the information associated with the candidate peptide.*" The Examiner probably did not fully appreciate the significance of the extended match concept. In the Specification (paragraph [0078]), as an example, an extended match is defined as a probabilistic function of a series of match characteristics, $E = (F, P, z, t, k, W, e)$, wherein:

- F is a fragment match (*see* paragraph [0071]),
- P is a peptide match (*see* paragraph [0070]),
- z is the charge used to match the experimental peptide m/z ratio with the candidate peptide mass (*see* paragraph [0072]),
- t is the elution time of the experimental parent peptide (*see* paragraph [0073]),
- k is the number of missed cleavages in the theoretical peptide matching the experimental data (*see* paragraph [0074]), and
- e is a vector of quantities obtained from other peptide identification systems, *e.g.*, commercial programs such as Sequest and Mascot (*see* paragraph [0075]).

Each of these match characteristics is considered a random variable having its own probability distribution under any given hypothesis. Therefore, the extended match E is also a random variable. The concept of extended match E is advantageous because it allows multiple match characteristics to be simultaneously considered in a systematic approach to score a match between an experimental peptide and a candidate peptide. The selection of the match characteristics (i.e., random variables) can be flexibly adapted to the available information from the MS/MS spectrum of the experimental peptide as well as the available information in the candidate peptide database. At the same time, the evaluation of multiple match characteristics

follows a disciplined methodology — the likelihood ratio is calculated based on a combination of individual probability distributions associated with the random variables, and therefore it is suitable for high-throughput MS/MS data processing. Neither Bafna nor Blumenfeld teaches or even suggests any extended match as presently claimed.

The Examiner asserts that the entire list of candidate peptide sequences that might have generated the experimental peptide's MS/MS spectrum is the extended match (Office Action at page 5, paragraph 8). This assertion results from a misinterpretation of the present invention. To further clarify the distinction, Applicants have amended claim 12 to recite, among other things, "*the extended match E being a probabilistic function of a tuple of random variables that include at least a fragment match and a peptide match between the experimental peptide and the candidate peptide.*" Bafna does not disclose, or even suggest, this feature at all. In its two-step stochastic process for generating MS/MS spectra, Bafna does not simultaneously consider multiple match characteristics in a mathematical framework of random variables and likelihood ratios. Bafna focuses on the generation of a fragmentation space having all the possible fragmentation patterns from a given candidate peptide, and then attempts to match the fragmentation patterns with the MS/MS spectrum of an experimental peptide. Apart from fragment match, no other match characteristics, such as parent peptide match or charge state match, are considered by Bafna at all, let alone in the form of random variables.

The Examiner also asserts that the disclosure of p-value in Bafna reads on H_1 (a hypothesis that the peptide sequence s is the correct sequence of the experimental peptide) and H_0 (a null-hypothesis that the peptide sequence s is an erroneous sequence of the experimental peptide) as recited in claim 12. This assertion is baseless. The p-value is typically used to measure the strength of the evidence against only the null hypothesis, wherein the smaller the p-

value, the stronger the evidence against the null hypothesis. The disclosure of the *p*-value in Bafna does not, by itself, require or suggest the evaluation of the alternative hypothesis at the same time. Unless Bafna contemplates the calculation of a likelihood ratio, there is no need for Bafna to evaluate both H_1 and H_0.

The Examiner further asserts that "since the scoring is generated from input MS/MS data and matching against a data of sequence as taught by Bafna et al., this reads on *D* (any extra information that is associated with the experimental peptide and the candidate peptide) as recited in claim 12. However, the Examiner has ignored the context in which the extra information is introduced. Unlike the present invention, Bafna does not teach or suggest a mathematical framework with which the extra information can be introduced to assist in scoring peptide matches. Therefore, even if Bafna wanted to include extra information, there is not a systematic way to accommodate it. Bafna aims at achieving a high-throughput process with minimal human intervention, and accordingly, Bafna focuses on fragmentation patterns as the sole match characteristic. Anything extra would cause Bafna's disclosed method to deviate from its stated goal of high-throughput functionality.

Regarding claim 13, the Examiner glossed over the part about random variables and asserts that Bafna's use of m/z data suggests "random variables that may be observable or derivable, and leads to the calculation of the extended match which results in a list of candidate sequences of varying rank of matching with the experimental sequence." Again, this assertion reflects a misunderstanding of the "extended match *E*" as presently claimed.

For the foregoing reasons, the combination of Bafna and Blumenfeld does not teach or suggest all the elements as presently claimed.

The combination of Bafna with Blumenfeld is improper as well. Blumenfeld discloses the use of likelihood ratio in an entirely different field. Applicants do not deny that the use of likelihood ratio to evaluate hypotheses is well known among statisticians. Yet, prior to the present invention, there was no indication that likelihood ratios were ever applied, or even needed or desirable, in the field of peptide matches. From hindsight, one can probably recognize that likelihood ratios are beneficial or applicable to scoring peptide matches. However, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Such desirability of the combination cannot be found in Blumenfeld as it does not even concern peptide matches. Bafna does not provide the motivation to combine, either. While Bafna recognizes that "good scoring is essential for eliminating false positives," that statement is nothing more than a general aspiration to improve peptide matching techniques. It does not necessarily lead one of ordinary skill to take any particular approach to improve scoring methods for peptide matches.

To further distinguish the present invention from the cited references, Applicants have added claim 59, which recites, among other things, "*the extended match E being a probabilistic function of a tuple of random variables that include at least a consecutive fragment match between the experimental peptide and the candidate peptide*" and "*the stochastic model incorporating a probability distribution of each of the random variables, wherein the probability distribution associated with the consecutive fragment match is determined based on a Hidden Markov Model.*" Since neither Bafna nor Blumenfeld mentions any consecutive fragment matches or Hidden Markov Model, claim 59 is also patentable over these references.

In view of the foregoing, it is respectfully requested that the aforementioned obviousness rejection of claims 12-15 and 18-24 be withdrawn.

V. CONCLUSION

In view of the foregoing, it is respectfully submitted that the present application is in condition for allowance, and an early indication of the same is courteously solicited. The Examiner is respectfully requested to contact the undersigned by telephone at the below listed telephone number, in order to expedite resolution of any issues and to expedite passage of the present application to issue, if any comments, questions, or suggestions arise in connection with the present application.

To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made.

Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account No. 50-0206, and please credit any excess fees to the same deposit account.

Respectfully submitted,

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Dated: March 21, 2007

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